Matching-Adjusted Indirect Comparisons of Avapritinib Versus Midostaurin for the Treatment of Patients with Advanced Systemic Mastocytosis

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Objectives

- Advanced systemic mastocytosis (AdvSM) is a rare haematological condition characterized by abnormal growth and accumulation of mast cells in a patient's internal organs and tissues[1]
- Patients with AdvSM experience severe and life-threatening symptoms (such as organ damage) that decreases overall survival and affects quality of life
- Only two therapies are approved for use in all subtypes of AdvSM: avapritinib (approved in the US in June 2021) and midostaurin (approved in the US and the EU in 2017)[2-4]
- Given the rare nature of AdvSM and the lack of head-to-head studies, an understanding of the comparative efficacy of these two therapies would help inform decision-making by healthcare professionals and payers
- Our objective was to estimate the relative efficacy of avapritinib versus midostaurin in the treatment of patients with AdvSM, using matching-adjusted indirect comparison (MAIC) methodology

Methods

Evidence Base

- A clinical systematic literature review performed in January 2021 examined the clinical evidence for the treatment of AdvSM published in MEDLINE® In-Process (using Pubmed.com); Embase® and MEDLINE (using Embase.com); the Cochrane Library; and proceedings from relevant conferences
- Additional inclusion and/or exclusion criteria were applied to the literature search results to identify studies that:
  - Investigated either avapritinib or midostaurin
  - Had a sample size of >10 patients
  - Were clinical trials (not observational studies)

Indirect Treatment Comparisons

- As AdvSM is a rare disease and no randomized head-to-head or placebo-controlled clinical trials have been conducted to date, we used unanchored MAIC methods to estimate the relative effect of avapritinib and midostaurin[5-7]
  - MAIC methods can be used to adjust for between-trial differences in baseline patient characteristics in the absence of randomization
- The variables used in the weighting were based on those identified as important prognostic factors through exploratory subgroup analyses of the avapritinib patient-level data, but were limited to those reported in the comparator evidence
  - The baseline characteristics considered were age, gender, race, Eastern Cooperative Oncology Group Performance Status (ECOG PS), prior systemic therapy, AdvSM subtype, *KIT* D816V mutation status, bone marrow mast cell burden, serum tryptase level, and number of C-findings (which are used to assess organ damage in AdvSM as per World Health Organization)
- The primary endpoint of interest for this research was overall survival (OS)
  - Comparisons were also performed for overall response rate (ORR) and complete remission (CR) as assessed by the International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria[8]
- Sensitivity analyses were performed for the avapritinib population who were midostaurin naïve (to compare like-for-like populations), the avapritinib population who had received the recommended 200 mg starting dose of avapritinib, and the population who had received prior systemic therapy[9,10]

Results

Evidence Base

- The systematic literature review identified four relevant single-arm trials: two that investigated avapritinib (EXPLORER and PATHFINDER) and two that investigated midostaurin (D2201 and A2213)
  - Both D2201 and A2213 were multicentre, single-arm, open-label, Phase II studies that evaluated the efficacy and safety of midostaurin in patients with AdvSM[11,12]
  - EXPLORER is a Phase I/II, open-label, single-arm trial that is divided into two stages: a dose-escalation stage (Part 1) and a dose-expansion stage (Part 2)[13,14]
  - PATHFINDER is an ongoing Phase II, open-label, single-arm trial evaluating the efficacy and safety of avapritinib (200 mg, once daily, starting dose) in patients with AdvSM[15]
- We considered it acceptable to pool data from the efficacy populations investigating the same treatment to decrease the uncertainty associated with small sample sizes[16]

Formulating the MAIC

- For OS, we identified the following variables as being potentially important prognostic factors and included them in the weighting: age (≤ median, > median in the comparator population), AdvSM subtype (systemic mastocytosis with associated haematological neoplasm [SM-AHN], aggressive systemic mastocytosis [ASM], and mast cell leukaemia [MCL]) and race (white, non-white)
- For ORR and CR, the additional variables of ECOG PS (< 2, ≥ 2), *KIT* D816V mutation status (positive, negative) and bone marrow mast cell burden (≤ median, > median in the comparator population) were included in the weighting
- The number of C-findings per patient also came up as potentially prognostic for all endpoints
  - However, due to the non-comparability of this covariate across the studies, it was not appropriate to use it in the weighting
- The patient characteristics that were used in the weighting are summarized across the four studies in Table 1

Table 1: Baseline characteristics used in the weighting

Study	EXPLORER	PATHFINDER	A2213	D2201
Treatment	Avapritinib	Avapritinib	Midostaurin	Midostaurin
Population	RAC-RE (N = 53)	RAC-RE (N = 32)	PEP (N = 26)	PEP (N = 89)
Age (years), median (range)	65 (34, 83)	68 (37, 85)	64.5 (24, 79)	64 (25, 82)
Race White, n (%)	47 (89)	32 (100)	21 (81)	86 (97)
ECOG PS, n (%)				
0/1	36 (68)	21 (66)	12 (46)	57 (64)
2/3	17 (32)	11 (34)	14 (54)	32 (36)
Subtype of AdvSM, n (%)				
ASM	3 (5.7)	2 (6.3)	3 (12)	16 (18)
SM-AHN	37 (69.8)	26 (81.3)	17 (65)	57 (64)
MCL	13 (24.5)	4 (12.5)	6 (23)	16 (18)
***KIT* D816V mutation status, n (%)**				
Positive	51 (96.2)	30 (93.8)	19 (73.1)	73 (82.0)
Negative	2 (3.8)	2 (6.3)	6 (23.1)	14 (15.7)
Other	0 (0.0)	0 (0.0)	1 (3.8)[a]	2 (2.2)[b]
Bone marrow mast cell burden (%), median (range)	50 (5, 95)	50 (10, 95)	50 (5, 95)	50 (8, 98)

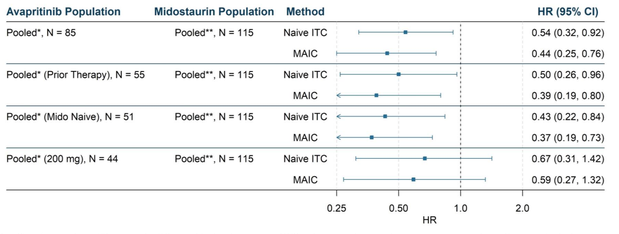
Key: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, full analysis set; MCL, mast cell leukaemia; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with associated haematological neoplasm.

Note: [a] The patient was positive for the *KIT* S451C mutation. [b]The *KIT* D816V mutation status was unknown.

Overall Survival Results

- The indirect treatment comparison (ITC) results (both MAICs and naïve ITCs) comparing avapritinib with midostaurin for OS are presented in Figure 1
- Across the analyses performed, avapritinib consistently lowered the hazard of death compared with midostaurin, with hazard ratios (HRs) ranging from 0.37 to 0.67
- Comparing the efficacy population of the avapritinib studies (n = 85) to the efficacy population in the midostaurin studies (n = 115), avapritinib roughly halved (44%) the risk of death for patients compared to midostaurin
- Overall, the weighting had little effect on OS as shown in Figure 2 where the weighted and unweighted Kaplan–Meier plots were very close to each other
- Sensitivity analyses were relatively consistent with the primary analysis, even if the uncertainty was increased by the smaller number of patients

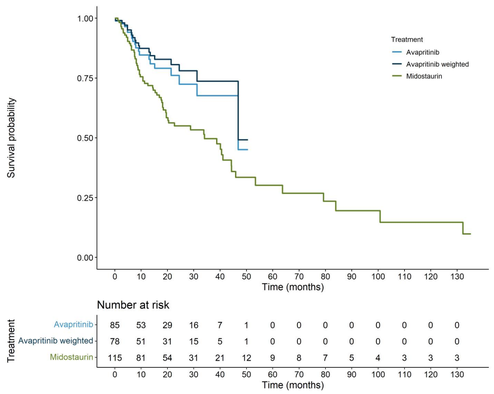
Figure 1: Forest plots to show the overall survival results



Key: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; mido, midostaurin; N, number of patients.

Notes: *Pooled PATHFINDER and EXPLORER population. **Pooled A2213 and D2201 population.

Figure 2: Kaplan–Meier plots of overall survival results



Overall Response Rate and Complete Remission Results

- ORR's and CR rates in the pooled PATHFINDER and EXPLOER population and D2201 are displayed in Table 2

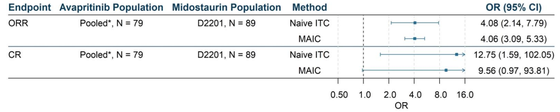
Table 2: Overall response rates and complete remission rates

Endpoint	Avapritinib responders (%)	Midostaurin responders (%)
ORR	69.62%	35.96%
CR	12.66%	1.12%

Key: CR, complete remission; ORR, overall response rate.

- ITC results for ORR and CR are displayed in Figure 3
- The results suggest that, compared with midostaurin, avapritinib was associated with a greater odds of a best response and CR (odds ratios [ORs] were all greater than 1)
- Patients treated with avapritinib were 4.06 times more likely to achieve a best response than patients treated with midostaurin
- Patients treated with avapritinib were 9.56 times more likely to achieve a CR than patients treated with midostaurin
  - However, it is difficult to draw conclusions from the CR comparison due to the small number of patients who achieved CR across the studies, which resulted in large confidence intervals around the ORs

Figure 3: Forest plots to show the overall response rate and complete remission results



Key: CI, confidence interval; CR, complete remission; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; N, number of patients; OR, odd ratio; ORR, overall response rate.

Note: *Pooled PATHFINDER and EXPLORER population.

Conclusions

Despite the limitations associated with unanchored MAICs, this research suggests that patients treated with avapritinib experienced meaningful improvements in survival and response (including ORR and CR) compared with midostaurin

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Disclosures

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